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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/581,471

08/31/2006

Philip J. Fay

176/61702

3888

26774

7590

05/08/2009

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EXAMINER

TSAY, MARSHA M

ART UNIT

PAPER NUMBER

1656

MAIL DATE

DELIVERY MODE

05/08/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/581,471	<b>Applicant(s)</b> FAY ET AL.	
	<b>Examiner</b> Marsha M. Tsay	<b>Art Unit</b> 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3-6,9,11-26,32-46 and 48-53 is/are pending in the application.
- 4a) Of the above claim(s) 11,14-18,23-26,32-46 and 48-52 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-6,9,12,13,19-22 and 53 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

Art Unit: 1656

This Office action is in response to Applicants' remarks received February 24, 2009.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Currently amended claim 11 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the instant claim is drawn to a chimeric Factor VIII that comprises substitution of one or more domains. The instant invention appears to be drawn to a recombinant Factor VIII comprising a point mutation at the A domain.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 11 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 2, 7-8, 10, 27-31, 47 are canceled. Claims 11, 14-18, 23-26, 32-46, 48-52 are withdrawn. Claims 1, 3-6, 9, 12-13, 19-22, 53 are currently under examination.

Priority: The request for priority to provisional application 60/526664, filed December 3, 2003, is acknowledged.

The declaration under 37 CFR 1.132 filed February 24, 2009, is sufficient to overcome the rejection of claims 1-6, 9, 11-13, 19-22 based upon Wakabayashi et al. (November 2003 "Residues 110-126 in the Factor VIII Heavy Chain contain a Ca<sup>2+</sup> Binding Site required for

Art Unit: 1656

cofactor activity.” *Blood, ASH Annual Meeting Abstracts*, 102(11): p. 542a, Abstract 1988; IDS 06.01.08).

## Objections and Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 9, 12-13, 19-22, 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a recombinant Factor VIII comprising an A1 domain that includes a point mutation in or near at least one calcium binding site of the A1 domain, wherein the Factor VIII has a specific activity higher than that of wild-type Factor VIII. *Vas-Cath Inc. V. Mahurkar*, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” As stated above, a recombinant Factor VIII comprising an A1 domain that includes a point mutation in or near at least one calcium binding site of the A1 domain, wherein the Factor VIII has a specific activity higher than that of wild-

Art Unit: 1656

type Factor VIII. The use of the term "includes" is interpreted to be the same as open language "comprising" allows for additional mutations, in addition to the recited point mutation in or near at least one calcium binding site of the A1 domain. However, the skilled artisan cannot necessarily envision the detailed structures of ALL the derivatives of Factor VIII comprising an A1 domain and comprising more amino acid substitutions in addition to the point mutation in or near at least one calcium binding site of the A1 domain, wherein the recombinant factor VIII has a higher specific activity than that of a wild-type Factor VIII because the specification provides minimal guidance as to which substitutions (i.e. conservative, unconservative) and which amino acids are essential and critical for the wild-type protein to have a higher specific activity, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods of making the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Claims 1, 3-6, 9, 12-13, 19-22, 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant Factor VIII comprising a point mutation at residue 113 of the A1 domain, wherein said Factor VIII has a higher specific activity than wild-type Factor VIII, does not reasonably provide enablement for all Factor VIII proteins comprising an A1 domain that includes a point mutation in or near at least one calcium binding site of the A1 domain that has a higher specific activity than wild-type Factor VIII. The

Art Unit: 1656

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art to ascertain which derivatives of Factor VIII comprising an A1 domain that includes a point mutation in or near at least one calcium binding site of the A1 domain will have a higher specific activity than that of wild-type Factor VIII. Claim 1 recites that said A1 domain includes at least a point mutation in or near at least one calcium binding site of the A1 domain. The use of the term "includes" is interpreted to be the same as open language "comprising" allows for additional mutations, in addition to the recited point mutation in or near at least one calcium binding site of the A1 domain. Thus there could be a myriad of variants which contain more substitutions (i.e. conservative, unconservative) in addition to the A1 domain that includes a point mutation in or near at least one calcium binding site of the A1 domain. Therefore, for the instant claimed invention, it would require an undue burden of experimentation for a skilled artisan to determine exactly which derivatives were active.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

Art Unit: 1656

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case the quantity of experimentation would be large since there are myriad substitutions (i.e. conservative, unconservative) to choose from. The amount of guidance in the specification is minimal with regard to which amino acids in Factor VIII are essential for activity or higher specific activity. Few working examples are present of Factor VIII with a point mutation in or near at least one calcium binding site of the A1 domain. The nature of the invention is such that many different proteins that are substantially similar to Factor VIII may or may not have biological activity or even higher biological activity. The state of the prior art is that even proteins that are 99% similar to the wild-type protein are at times not fully active. The relative level of skill in this art is very high. The predictability as to what substantially similar protein will have which activity is zero.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1656

Claims 1, 6, 9, 12-13, 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites a point mutation in or at least one calcium binding site of the A1 domain of a recombinant Factor VIII but does not provide a reference SEQ ID NO. Further, the amino acid sequence of Factor VIII from various species differs in length; therefore, it is unclear from which source and/or species the instant Factor VIII is from. Therefore, the claim is unclear as to which sequence needs to be used in order to make the point mutation since the A domain may not be located at the same numerical positions for each Factor VIII protein. Applicants are asked to amend the instant claim to include a SEQ ID NO. for the Factor VIII protein so that it is clear which amino acids and at which positions are mutated.

Claims 6, 9, 12-13, 19-22 are included in this rejection because they are dependent on claim 1 and fail to cure its defect.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



Art Unit: 1656

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/

Primary Examiner, Art Unit 1656

May 4, 2009